

REMARKS

1. Status of claims

Claims 1-23 and 129-130 are pending and under consideration. Claims 24-128 have previously been canceled.

2. Claim rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-7, 12-20, 22-23, and 129-130 as allegedly being obvious over Rajgarhia, *et al.*, US 2004/0029238 ("Rajgarhia") in view of Lee, *et al.*, UK 2251864. Applicants traverse this rejection.

The present claims are directed to methods of producing lactic acid by, *inter alia*, performing selection on a parent yeast strain containing an exogenous lactate dehydrogenase gene and culturing a resultant acid-tolerant yeast strain. Applicants disagree with the Examiner's repeated statements that Rajgarhia teaches "acid tolerant" yeast strains. Acid tolerance, as used by the present claims, is defined in the specification at p. 17, lines 25-26. Rajgarhia fails to teach yeast capable of producing lactic acid at a pH that is lower than the yeast's parent strain can; therefore, Rajgarhia's yeast are not "acid tolerant."

The Examiner alleged that it would have been obvious for the person of ordinary skill in the art to use a yeast having deleted pyruvate decarboxylase and expressing an exogenous LDH gene, as taught by Rajgarhia, in the *Lactobacillus* selection system taught by Lee.

We disagree with the Examiner's allegation for the following reasons. Under recent United States case law, specifically, *KSR International Co. v. Teleflex Inc.*, 550 U.S.—, 82 USPQ2d 1385 (2007), regardless of the particular rationale used, a finding of unpatentability requires an Examiner to show, among other findings, a finding that one of ordinary skill in the

art could have pursued known options or combined known elements *with a reasonable expectation of success* at arriving at the claimed invention. A reasonable expectation of success is necessary even if the person of ordinary skill in the art would have been motivated to combine known elements. At most, the person of ordinary skill in the art, in attempting to apply the teachings of Rajgarhia to the *Lactobacillus* selection system taught by Lee, would have had an *unreasonable* expectation of success at arriving at the claimed invention.

Lee teaches selection of *Lactobacillus* by culturing a mixed population of *Lactobacillus* in a milk medium at a pH from about 3.4 to 4.2, with the removal of medium and cells and the addition of fresh, pH 6.2-6.5, medium when the culture pH is below 3.8 (p. 3, line 14 to p. 8, line 18). The person of ordinary skill in the art is aware that *Lactobacillus* express an *endogenous* LDH gene. Lee does not teach culturing a yeast expressing an exogenous LDH gene (i.e., an LDH gene from another species) in a minimal medium. The person of ordinary skill in the art would expect that yeast and *Lactobacillus* have differences in their ability to maintain their viability at low pH values (in light of the yeast being eukaryotes and *Lactobacilli* being prokaryotes; also in light of the different environments to which yeast and *Lactobacilli* have adapted during their evolution), and in their ability to grow and produce lactic acid in milk medium versus minimal medium. The person of ordinary skill in the art would also expect that yeast expressing an exogenous LDH gene would express it under the control of a different promoter, under the influence of eukaryote-specific control mechanisms, and on a different chromosome, plasmid, or other replicable DNA molecule than would be the case in *Lactobacillus*. The person of ordinary skill in the art would therefore not expect to select acid tolerant yeast expressing an exogenous LDH gene by using the milk medium and selection techniques taught by Lee with any reasonable expectation of success.

Further, with regard to claims 129-130, Lee also does not teach lowering the medium pH during the selection process. Lee's selection system adds fresh milk medium at pH 6.2-6.5, which has the effect of raising the pH of the *Lactobacillus* culture on which selection is being performed. For this additional reason, the person of ordinary skill in the art would therefore not expect to select acid tolerant yeast by using the techniques taught by Lee with any reasonable expectation of success at achieving the invention of claims 129-130.

In addition, with regard to claims 3-4 and others reciting production of lactic acid at a pH of less than about 2.8, such as less than about 2.3, Lee's selection system only yields *Lactobacillus* able to produce lactic acid at a pH of 3.4 (p. 3, lines 26-33). Even without the differences between yeast and *Lactobacillus* and milk medium versus minimal medium, the production of lactic acid at a pH of less than about 2.8 is beyond the reasonable expectation of the person of ordinary skill in the art. For this additional reason, the person of ordinary skill in the art would therefore not expect to select acid tolerant yeast capable of producing lactic acid at the pH values of claims 3-4 by using the techniques taught by Lee with any reasonable expectation of success.

In light of the teachings of the references and the knowledge of the person of ordinary skill in the art, such a person could not have had a reasonable expectation that acid tolerant yeast could be prepared and lactic acid produced by use of the yeast taught by Rajgarhia undergoing selection according to the *Lactobacillus* selection techniques of Lee. Rajgarhia and Lee together *fail* to provide the person of ordinary skill in the art with any reasonable expectation either acid tolerant yeast would be generated or lactic acid produced. Therefore, they fail to render the present claims unpatentable under any standard requiring a finding of a reasonable expectation of

success set forth by the court in *KSR*. Therefore, claims 1-7, 12-20, 22-23, and 129-130 are patentable over the references of record and this rejection should be withdrawn.

The Examiner also rejected claim 8 as being unpatentable over Rajgarhia in view of Lee, as discussed above, and further in view of Hause, *et al.*, US 2003/0228671 ("Hause"). Applicants traverse this rejection.

Rajgarhia and Lee have been discussed above. Hause reports that a yeast strain produced lactic acid without producing glycerol (paragraph [0209]). Again, the Examiner alleges Hause's yeast are "acid tolerant," but they too fail to meet the definition of acid tolerance made in the specification at p. 17, lines 25-26. Regardless, whether or not Hause teaches a yeast strain producing lactic acid without producing glycerol, this teaching fails to supplement the failure of Rajgarhia in view of Lee to select for acid tolerant yeast strains using the *Lactobacillus* selection techniques of Lee.

In light of the teachings of the references and the knowledge of the person of ordinary skill in the art, such a person could not have had a reasonable expectation that acid tolerant yeast producing less than 1 ppm glycerol could be prepared and lactic acid produced by use of the yeast taught by Rajgarhia or Hause undergoing selection according to the *Lactobacillus* selection techniques of Lee. Rajgarhia, Lee, and Hause together *fail* to provide the person of ordinary skill in the art with any reasonable expectation either acid tolerant yeast would be generated or lactic acid produced. Therefore, they fail to render the present claims unpatentable under any standard requiring a finding of a reasonable expectation of success set forth by the court in *KSR*. Therefore, claim 8 is patentable over the references of record and this rejection should be withdrawn.

In addition, the Examiner rejected claim 21 as being unpatentable over Rajgarhia in view of Lee, as discussed above, and further in view of Rajgarhia, *et al.*, US 2004/0029256 ("Rajgarhia '256"). Applicants traverse this rejection.

Rajgarhia and Lee have been discussed above. Rajgarhia '256 reports that a yeast strain expressing an exogenous LDH of *Lactobacillus plantarum* produced lactic acid (claim 10). Again, the Examiner alleges Rajgarhia '256's yeast are "acid tolerant," but they too fail to meet the definition of acid tolerance made in the specification at p. 17, lines 25-26. Regardless, whether or not Rajgarhia '256 teaches a yeast strain expressing an exogenous LDH of *L. plantarum*, this teaching fails to supplement the failure of Rajgarhia in view of Lee to select for acid tolerant yeast strains using the *Lactobacillus* selection techniques of Lee.

In light of the teachings of the references and the knowledge of the person of ordinary skill in the art, such a person could not have had a reasonable expectation that acid tolerant yeast could be prepared and lactic acid produced by use of the yeast taught by Rajgarhia or Rajgarhia '256 undergoing selection according to the *Lactobacillus* selection techniques of Lee. Rajgarhia, Lee, and Rajgarhia '256 together *fail* to provide the person of ordinary skill in the art with any reasonable expectation either acid tolerant yeast would be generated or lactic acid produced. Therefore, they fail to render the present claims unpatentable under any standard requiring a finding of a reasonable expectation of success set forth by the court in *KSR*. Therefore, claim 21 is patentable over the references of record and this rejection should be withdrawn.

Finally, the Examiner rejected claims 9-10 as being unpatentable over Rajgarhia in view of Lee, as discussed above, and further in view of Porro, *et al.*, US 7,049,108 ("Porro"). Applicants traverse this rejection.

Rajgarhia and Lee have been discussed above. Porro reports a *Saccharomyces cerevisiae* strain expressing an exogenous LDH of *Bacillus megaterium* and having deleted PDC genes so that it produces no ethanol. Whether or not Porro teaches such an *S. cerevisiae* strain, this teaching fails to supplement the failure of Rajgarhia in view of Lee to select for acid tolerant yeast strains using the *Lactobacillus* selection techniques of Lee.

In light of the teachings of the references and the knowledge of the person of ordinary skill in the art, such a person could not have had a reasonable expectation that acid tolerant yeast could be prepared and lactic acid produced by use of the yeast taught by Rajgarhia or Porro undergoing selection according to the *Lactobacillus* selection techniques of Lee. Rajgarhia, Lee, and Porro together *fail* to provide the person of ordinary skill in the art with any reasonable expectation either acid tolerant yeast would be generated or lactic acid produced. Therefore, they fail to render the present claims unpatentable under any standard requiring a finding of a reasonable expectation of success set forth by the court in *KSR*. Therefore, claims 9-10 are patentable over the references of record and this rejection should be withdrawn.

3. *Allowable subject matter*

The Examiner indicated claim 11 is allowable.

4. *Conclusion*

Applicants submit all pending claims are in condition for allowance. The Examiner is invited to contact the undersigned patent agent at (713) 934-4065 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

WILLIAMS, MORGAN & AMERSON, P.C.
CUSTOMER NO. 79138

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/Raymund F. Eich/
Raymund F. Eich, Ph.D.
Reg. No. 42,508

10333 Richmond, Suite 1100
Houston, Texas 77042
(713) 934-4065
(713) 934-7011 (fax)

AGENT FOR APPLICANTS